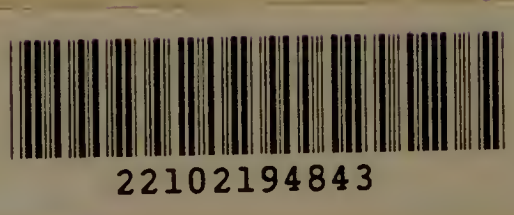

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CHAPTER III.

EXAMINATION OF THE BLOOD.

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I. THE SCOPE OF HEMATOLOGY IN SURGERY.

It is a well-established fact that hematology, if sanely interpreted, is of real value in surgical practice. Weighed as a bit of clinical evidence, the blood report may give either the essential clue to a puzzling group of symptoms, or at least confirm other symptoms and thus complete a picture of disease. But regarded as an infallible sign, affording a specific diagnosis of a given disease, the results of the blood examination are more often misleading than useful. Positive findings with the serum test, with blood culturing, and with search for hemamœbæ settle the diagnosis without further inquiry, as also does the detection of the characteristic leukocyte formula in leukemia and of the distinctive megaloblastic cell changes in pernicious anemia, but these comparatively infrequent findings are of greater interest to the internist than to the surgeon. To the latter the questions of hemoglobin values, the leukocyte count, iodophilia, the coagulation time, bacteriemia, and, perhaps, cryoscopy are important clinical side-lights applicable to routine surgical practice. Negative reports from blood examinations have, at the best, an uncertain value, and, though significant, are not to be depended upon with too much confidence—an abdomen reeking with pus is not invariably incompatible with a normal leukocyte count; failure to culture organisms from the circulating blood by no means rules out sepsis. "Correlate the blood report with the other clinical symptoms" is the maxim for the surgeon to remember, if he would derive from this method of research reliable information of diagnostic and prognostic application.

In this chapter it will be noted that several conditions not strictly of a surgical nature have been described—enteric fever, the primary anemias, the protozoan infections. This has been done for the sake of differential diagnosis, for who, ignorant of their different blood pictures, can apply hematology to the differentiation of such conditions as typhoid fever, malarial fever, and sepsis, cancer and pernicious anemia, leukemia and sarcoma of the spleen, and numerous other diseases having different blood formulas? The salient principles of blood histology and pathology have also been briefly referred to, as essential to the proper reading of that part of the text relating to surgical hematology. Technical methods of blood examination are not germane to the plan of this chapter, and are therefore omitted.

II. GENERAL PHYSIOLOGY AND PATHOLOGY OF THE BLOOD.

General Composition of the Blood.—Normal human blood is composed of fluid and cellular elements, the former constituting three-fifths and the latter two-fifths of its total volume, which in the adult represents from one-thirtieth to one-sixteenth of the body-weight, according to Haldane and Smith.[5] The blood is alkaline in *reaction*, the normal figures ranging from about 200 to 300 mgm. NaOH, and, according to some investigators, even beyond these limits. Permanent changes in the blood reaction probably do not occur so long as the emunctory organs act adequately. Decreased alkalinity is commonly found in the severe anemias and cachexias, in uremia, diabetes mellitus, and cholemia, in Asiatic cholera, in many of the dermatoses, and after chloroform narcosis. Up to the present time alkalimetry of the blood has been of laboratory rather than of clinical interest. The *specific gravity* of the blood varies from 1.055 to 1.065 in the healthy male adult, but is somewhat lower in the female and in the child. The specific gravity is temporarily increased by factors which tend to inspissate the blood—fasting, diarrhea, sweating, emesis, pyrexia, and cyanosis; it is decreased whenever the blood mass is diluted, as in anemia, after the injection of normal salt solution, and following the ingestion of a large volume of liquid. In a general way the specific gravity corresponds to the richness of the blood in hemoglobin and erythrocytes, but it is not a sure quantitative index to these constituents. Clinically, specific gravity testing is far more complicated and less accurate than hemoglobinometry.

The fluid constituent of the blood, the *plasma* or *liquor sanguinis*, is a clear yellowish fluid, of a specific gravity ranging between 1.026 and 1.030, and containing about 10 per cent. of solids, chiefly proteids. *Serum*, a product of coagulation, is a pale straw-colored fluid, having practically the same density and amount of solids as the plasma, from which it differs chiefly in containing fibrin ferment instead of fibrinogen. The principal *salt* of the blood is sodium chlorid, the others being in the form of sulphates and the salts of potassium, magnesium, and calcium. The *gases* of the blood, of which approximately sixty volumes are contained in each one hundred volumes of the whole blood, are oxygen, carbon dioxid, and nitrogen, the first existing chiefly in the hemoglobin of the erythrocytes, the second occurring as carbonates, and the last being held in simple solution. Among the *extractives* of the blood are urea, cholesterin, creatin, xanthin, sugar, and fats.

The most important *cellular elements* of the blood are the erythrocytes or red corpuscles and the leukocytes or white corpuscles. The blood plaques and the hemokonia may be classed with the blood cells, although these bodies probably are not histologic entities.

Coagulation and Fibrin.—Extravascular coagulation, due to an obscure interaction of fibrinogen, a ferment, and a calcium salt, separates the blood mass into two distinct portions, a gelatinous clot or *crassamentum*, and a fluid, *serum*. The clot consists of a mass of fibrin in the delicate meshes of which the blood cells are imprisoned; the serum is sim-

ply blood plasma minus the elements from which the clot-fibrin was evolved. In a vesselful of slowly coagulated blood the clot may show two clean-cut strata—a lower deep red layer of erythrocytes, and an upper yellow-gray zone of leukocytes, which constitutes the *buffy coat* of the clot, so frequently referred to by the older pathologists.

Hematopexis.—The term *hematopexis* has been coined by W. W. Keen to express the coagulation time of the blood. Normal blood coagulates within from three to six minutes after having been shed,* but in a number of pathologic states the coagulation time is either delayed or hastened. Hematopexis is considerably *delayed* in many cases of jaundice, anemia, anasarca, hemoglobinemia, hemophilia, purpura, asphyxia, acute alcoholic poisoning, and other toxic conditions. Marked delay in clotting occurs in poisoning by cobra venom and in mild cases of daboia poisoning, but in an individual inoculated with an excessive amount of the latter venom fatal intravascular clotting may be excited. Hirudin, a leech extract, has a remarkable effect in preventing both intravascular and extravascular coagulation. According to Bodong's experiments,[1] blood once hirudinized never regains its clotting power, and blood beginning to coagulate at once ceases to do so on the addition of hirudin. Permanent fluidity of the blood *in vitro* has also been observed in fatal poisoning by prussic acid.[2]

The coagulation time of the blood in jaundice appears to depend not upon the jaundice *per se*, but rather upon such attendant factors as toxemia, hemoglobinemia, and excessive anemia. Fatal post-operative hemorrhage has occurred in cases of malignant disease of the biliary passages with jaundice, but, on the other hand, in the obstructive jaundice of cholelithiasis this accident seems not to have been encountered. In purpura the clot, though formed, is imperfectly retracted and the serum is proportionately scanty (Sicard[3]). In the early days of an attack of enteric fever an appreciably delayed coagulation may predispose to intestinal hemorrhage, while in the later stages of this infection the clotting time may be so rapid as to favor thrombosis. This tendency to rapid coagulation is believed to be due to the excessive quantity of calcium salts in the blood of the convalescent typhoid, since an unduly large amount of lime salts is necessarily ingested by a patient kept for weeks upon a milk diet. As a preventive of thrombosis Wright and Knapp[4] suggest partial decalcification of the milk, by the addition of sodium citrate, as soon as the danger of intestinal hemorrhage is past.

Coagulation is *accelerated* by the administration of calcium salts in small doses, but if the dose be too large or if its use be continued too long, just the opposite effect is produced. From 60 to 90 grains daily of calcium chlorid for three or four days is the proper treatment to promote clotting in a patient whose coagulation time is delayed. Gelatin acts similarly, but much more feebly and erratically than calcium, for which it is but an indifferent substitute. Aside from its uncertain action, the possibility that tetanus spores may lurk in a gelatin solution should make one hesitate

*Here may be noted Wright's statement ("Brit. Med. Jour.," 1902, ii, 1706), thus far uncorroborated, that in the healthy male adult clotting may, in the exceptional instance, fail to occur for as much as fifteen minutes.

in selecting this substance for hypodermatic use in the treatment of hemorrhage. W. J. Taylor[6] believes that the use of thyroid extract internally promotes coagulation, and that the drug promises to be of great value to the surgeon in combating hemorrhage. While thyroid extract decidedly hastens the clotting of blood whose hematopexis is unduly slow, it appears to have no such effect on blood which coagulates normally. The most certain results are obtained by administering the dried extract, in doses of nine grains daily, for from three to seven days before operation.

Hyperinosis, or an increase in the amount and density of the fibrin network, is usually found in acute inflammatory febrile diseases, especially in those accompanied by sero-fibrinous and by purulent exudates. According to Hayem,[7] the density of the fibrin network roughly indicates the degree of the individual's resisting powers against infection. Abscess, pleural effusion, croupous pneumonia, rheumatic fever, peritonitis, erysipelas, variola, and influenza are examples of febrile infections in which hyperinosis occurs. As a rule, hyperinosis and inflammatory leukocytosis (*q. v.*) coexist, though exceptions are to be found in malignant disease and in purpura, in which conditions leukocytosis unattended by a fibrin increase is commonly detected; in influenza, on the contrary, there is a normal leukocyte count with decided hyperinosis. That all febrile states do not imply a fibrin increase is shown by the normal condition of the fibrin, if not, indeed, by the hypinosis, occurring in the pyrexias of grave primary anemias.

Hypinosis means a deficiency in the quantity of fibrin. Fibrin is not increased in malignant disease, tuberculosis, the malarial fevers, enteric fever, purpura, and the primary anemias, and occasionally a decided hypinosis occurs in these conditions.

The Freezing-point of the Blood.—Cryoscopy, or the process of estimating the freezing-point of liquids, has been applied to the blood and urine, with the object of determining their molecular concentration. Surgically, cryoscopy has been used chiefly in gaging the integrity of the kidneys. The freezing-point (expressed by the symbol $\triangle$) of normal blood ranges between —0.56° and —0.58° C., while normal urine freezes between —0.9° and —2° C. Korányi's pioneer work[8] showed that in diseases of the kidneys involving renal insufficiency the $\triangle$ of the blood falls and that of the urine correspondingly rises, these changes being due to the surcharging of the blood with excrementitious matter which the crippled kidneys fail to discharge. Single nephrectomy, he found, does not affect the normal $\triangle$ of the blood and urine, but double nephrectomy lowers the $\triangle$ of the former and raises the $\triangle$ of the latter. Kümmel,[9] and later Rumpel,[10] Lindeman,[11] and others, are responsible for the current impression that nephrectomy is contraindicated when the $\triangle$ of the blood is —0.6° C. or lower and the $\triangle$ of the urine is 1° C. or higher, the presumption being that when these figures are attained both kidneys are implicated too extensively to insure adequate elimination if one kidney is removed. That this impression needs revision has been shown recently by Loeb and Adrian[12] and by Rovsing,[13] who find that unilateral renal lesions may cause decided abnormalities of the $\triangle$, while, on the other hand, bilat-

eral disease may exist with no such changes. It is of clinical interest to know that the △ of blood rises in uremia, nephritis, pneumonia, hemoglobinemia, cyanosis, and high-grade anemia. Cystitis and pyelitis do not alter the blood's △.

Since the molecular concentration of the blood may be exaggerated by circulatory stasis, dependent upon cardio-vascular and hepatic diseases, abdominal neoplasms and like factors, all such causes of vascular embarrassment must be excluded before interpreting the findings of the cryoscope. Any departure from the normal should compel a careful revision of all the symptoms before deciding upon surgical interference, but cryoscopy alone is of doubtful value in determining the state of renal activity; it can afford no certain clue to the compensatory hypertrophy which a kidney may undergo. This question, together with other clinical features of cryoscopy, has been ably treated by Casper and Richter,[14] by Tinker,[15] and by Ogston.[16]

Hemoglobin.—Hemoglobin occurs in the stroma of the erythrocytes as oxyhemoglobin, an albuminous and ferruginous substance readily yielding oxygen to the tissues and highly susceptible to union with various gases, such as carbon monoxid and carbon dioxid. Hemoglobin is derived chiefly from the iron ingested in the form of food; but should this source of supply be cut off, it may be formed from the iron stored up in the liver and other organs. Iron is the most useful blood-builder for patients deficient in hemoglobin; arsenic, though it indirectly stimulates hemogenesis, has little or no effect in exciting a hemoglobin increase. (Aporti;[17] Bergmann;[18] Baumann.[19])

The *absolute amount* of hemoglobin is about 14 grams in each 100 grams of blood, this figure corresponding to the normal percentage of hemoglobin, arbitrarily fixed at 100. The term *color index* (valeur globulaire; blood quotient) means the proportionate amount of hemoglobin in each erythrocyte, the normal standard, calculated by dividing the hemoglobin percentage by that of the erythrocytes, being 1.00. If, as is commonly the case in chlorosis, the hemoglobin loss greatly exceeds that of the cells, the color index falls decidedly below normal—to 0.50 or lower; if, as is the rule in pernicious anemia, the cellular deficiency greatly outstrips the hemoglobin loss, the color index rises above normal—to 1.25 or perhaps higher; and if, as in the average case of secondary anemia, the hemoglobin and cellular losses are roughly proportionate, the color index deviates but slightly from the normal figure.

Oligochromemia, or diminution in the percentage of hemoglobin, is a blood finding common to all anemic states, and is associated usually with a more or less conspicuous decrease in the number of erythrocytes. Strikingly low hemoglobin percentages are found in chlorosis, in pernicious anemia, and in the anemias secondary to hemorrhage, sepsis, and malignant disease. These average findings in 150 consecutive cases of anemia illustrate the differences in the hemoglobin content in anemias of different origin:

Pernicious Anemia:	average	loss	in	50	cases	....	74.5	per cent.
Chlorosis:	"	"	"	"	"	....	56.8	" "
Secondary Anemia:	"	"	"	"	"	....	44.8	" "

The symptomatic anemias attending the chronic constitutional diseases, the infections, the hemorrhagic disorders, and the various toxic states also involve considerable diminution in the hemoglobin.

Moderate oligochromemia develops after anesthesia by ether and by chloroform, the loss generally being more pronounced the lower the preanesthetic hemoglobin figure. This fact accounts for the prevalent belief, popularized by Bierfreund,[20] that a hemoglobin percentage below 30 or 40 contraindicates general anesthesia. In cases of imperative necessity this arbitrary rule, of course, must be disregarded, but in other instances it is wiser to postpone the anesthesia until the hemoglobin loss has been restored by the use of iron, or to substitute a local for a general anesthetic. That Bierfreund's dictum is by no means invariably true is shown by the numerous reports of successful operations under general anesthesia in subjects with hemoglobin percentages ranging between 15 and 30.[21] Hutchins[22] has recently reported 60 operative cases with hemoglobin figures of 50 or less, in none of which did the etherization prolong or unduly aggravate the anemia.

Splenectomy and double oöphorectomy are followed by lower hemoglobin figures than the mere post-operative blood loss appears to warrant. A hemoglobin percentage 10 to 15 points below the normal standard is physiologic in women just before the onset of menstruation, with the full establishment of which this preliminary oligochromemia promptly disappears.

In the interpretation of the hemoglobin value it must be remembered that factors of blood concentration may account for abnormally high figures, while in diluted, hydremic blood the reverse occurs, the gain or loss in either instance paralleling the fluctuations of the erythrocytes. (See "Polycythemia," p. 121.)

Hemoglobinemia, or the presence in the blood plasma of hemoglobin dissolved from the erythrocytes, may be due to actual cellular destruction (hemocytolysis) or to a simple disunion of the hemoglobin and the cellular stroma and its escape from the latter into the plasma. In hemoglobinemia the whole blood loses its normal opacity and becomes decidedly transparent, and the serum is tinged a clear ruby-red color ("laked" blood). Prominent causes of hemoglobinemia, and, in extreme cases, of hemoglobinuria, include sepsis and many of the acute specific infections, various chronic cachexias, the hemorrhagic disorders, Raynaud's disease, and those obscure diseases known as epidemic hemoglobinuria and paroxysmal hemoglobinemia. Insolation, severe burns, extensive frostbite, and the transfusion of alien blood also liberate hemoglobin from the cells. The administration of the so-called "blood-poisons" in toxic amounts (especially the coal-tars, chlorates, iodids, mercury, nitrites, and strong acids) may account for active erythrocyte disintegration and consequent hemoglobinemia, as also may other toxic substances such as snake and scorpion venoms and certain of the vegetable poisons.

Methemoglobinemia is characterized by the presence of methemoglobin in the erythrocytes, this abnormal pigment being a modified form of oxyhemoglobin in which the oxygen is so firmly incorporated with the cells

that their oxygenating powers are inhibited. Like hemoglobinemia, methemoglobinemia is produced by poisoning with the coal-tars, iodids, and nitrites, as well as by a number of other less familiar toxic substances. The same change has also been observed in malignant edema, purpura hemorrhagica, and Addison's disease.

Carbon monoxid hemoglobin is a blood change occurring in coal-gas poisoning and in the asphyxia due to the fumes of fire-damp. The change is betrayed by a bright cherry-red color of the blood, both arterial and venous.

Anemia.—The word anemia expresses a deficiency, quantitative, qualitative, or both, in the amount of the blood. A quantitative anemia, or *oligemia*, may exist with no alteration in the composition of the several constituents of the blood, although it generally involves a diminution in the cells and in the solids of the plasma. The best surgical illustration of a quantitative anemia is the deficiency in the volume of the blood immediately after an extensive traumatic hemorrhage. *Ischemia* is a local anemia, due to interference with the blood-supply of a circumscribed area of the body. A dilution of the blood, relatively increasing its liquid elements, constitutes *hydremia*, this change being common to the various anemias, and occurring also as the result of dropsy, of extreme vasomotor dilatation, and of the ingestion or the injection of large quantities of fluids. *Anhydremia*, or an inspissation of the blood, is characterized by a relative diminution in the liquids, this change being due to drains upon the body-fluids (diarrhea, urinary crises, emesis, sweating, and effusions) and, to a moderate degree, to increased arterial tension. *Pseudoanemia* is a spurious anemia, in which the objective signs of anemia exist and yet examination shows a normal blood picture. This apparent blood deterioration is best explained by such factors as hereditary peculiarities, vasomotor disturbances, and anomalies of the pigment and the capillary network of the skin. The "prison bleach" of the convict and the peculiar pallor of the resident in the tropics do not necessarily signify an actual blood poverty.

Owing to our uncertain knowledge of blood pathology, it is necessary arbitrarily to classify all forms of anemia as *primary* or *essential*, and as *secondary* or *symptomatic*. The primary anemias are those in which the etiology is either obscure or insufficient to account for the blood changes, which are attributed to grave lesions of the blood-making organs, this group including chlorosis, pernicious anemia, lymphatic and myelogenous leukemia, Hodgkin's disease, and perhaps splenic anemia. The secondary anemias comprise those with a perfectly clear etiology and without essential involvement of the blood-making apparatus. They include the anemias secondary to hemorrhage, inanition, faulty hygiene, intestinal parasites, metal poisoning, acute infections, and the cachexias incident to many chronic diseases. To the surgeon the anemias of greatest practical interest are those secondary to hemorrhage, suppuration, sepsis, and malignant disease.

Primary Anemia.—*Chlorosis.*—This disease is characterized by a hemoglobin loss greatly disproportionate to that of the erythrocytes, and

therefore productive of a low color index, since the cells individually are deficient in their hemoglobin content. The erythrocytes are generally decreased in diameter, but they rarely show marked structural degeneration, and erythroblasts, save for an occasional normoblast in severe cases, are not found. The number of leukocytes is not increased, but a relative lymphocytosis and a subnormal number of eosinophiles are common findings. Other changes include an increase in the volume of the plasma with a diminution in the oxygen capacity of the blood unit (Lorrain Smith,[23] Lloyd Jones[24]), and a striking deficiency in the quantity of blood albumin (Biernacki[25]). Since several other conditions (notably syphilis, tuberculosis, and chronic nephritis) may provoke a so-called "chlorotic" state of the blood, hematology must be supplemented by other clinical methods in the diagnosis of chlorosis.

Pernicious Anemia.—The erythrocyte decrease is strikingly disproportionate to the hemoglobin loss, so that a high color index is the rule, owing to a relative excess of hemoglobin in the individual cells. The erythrocytes are much distorted, show granular degeneration, and are generally increased in diameter. In typical cases there are numerous megaloblasts and normoblasts, the former type of cells predominating—the so-called "megaloblastic blood picture." The number of leukocytes is either normal or subnormal, and a relative lymphocytosis, together with the presence of a few myelocytes, can usually be detected. The blood volume fluctuates in different cases, but a true general increase is unlikely. The total oxygen capacity of the blood is greatly diminished (Lorrain Smith[26]). The albumin content of the whole blood is decidedly subnormal (Gumprecht and Stintzing[27]), although the serum albumin is but moderately reduced (Diabella[28]). Pernicious anemia differs from *chlorosis* and from *secondary anemia* in having a high color index, a prevalence of megalocytes and megaloblasts, and a decided leukopenia with relative lymphocytosis. The anemia of *Bothriocephalus latus* infection, which may precisely simulate pernicious anemia, promptly disappears after the expulsion of the parasites from the gut.

Leukemia.—In *lymphatic leukemia* the typical blood picture is one of lymphemia, or an absolute and a relative increase in the number of lymphocytes, these cells ordinarily constituting more than nine-tenths of the total leukocyte count, which may be twenty or thirty times in excess of the maximum normal standard. As a general rule, the more acute the case, the greater the tendency toward a large-celled lymphocytosis. Well-marked hemoglobin and erythrocyte losses, with correspondingly severe degenerative cellular changes, are also conspicuous. In *myelogenous leukemia* the characteristic blood change is known as myelemia, that is, the presence of large numbers of myelocytes in the circulating blood. This type of marrow cell constitutes about one-fifth of the total leukocyte count, which is ordinarily forty or fifty times higher than normal. Mast cells are also very numerous, and the eosinophiles are increased. The hemoglobin and erythrocytes are diminished, and the cellular degeneration is usually of high grade; nucleated erythrocytes, the majority of which are normoblasts, are commonly found in large numbers. An *intercurrent infection* develop-

ing in a leukemic subject usually excites prompt and striking changes in the leukocytes, as well as in the other clinical manifestations of the disease. Generally the leukocytes rapidly fall toward the normal, both quantitatively and qualitatively; sometimes the leukemic blood picture is exaggerated; and exceptionally little or no change takes place. In the first class of cases the fall of the leukocytes is accompanied by a marked improvement in the other symptoms, but with recovery from the complicating disease the blood resumes its leukemic hall-mark and the other evidences of leukemia return. Sepsis, pneumonia, erysipelas, acute tuberculosis, and malignant disease are typical examples of infections acting in this manner, for the details of which Dock's careful résumé [29] should be consulted.

In contrast to lymphatic leukemia, the blood of the myelogenous variety shows a more moderate type of anemia but a greater number of normoblasts, and a much higher count of leukocytes, among which myelocytes, eosinophiles, and mast cells are conspicuous. In a high leukocytosis the *number* of leukocytes may be as great as in leukemia, but the polynuclear neutrophiles (not the lymphocytes nor the myelocytes) are the cells responsible for the increase. An *absolute lymphocytosis* (such as may occur in pertussis, in infantile pneumonia, or in lymphosarcoma), by involving a high absolute and relative lymphocyte increase, may resemble lymphatic leukemia; in this sort of lymphocytosis, however, the increase is moderate and temporary, the anemia is not usually marked, and the etiologic factors are sufficiently conclusive. *Chloroma, multiple periostitis,* and *Still's disease* all are clinically not unlike leukemia; in the first-named disease the differentiation must often be made by the objective symptoms, since the blood changes may resemble those of lymphatic leukemia; in the second, which, hematologically, counterfeits myelogenous leukemia, the distinctive history is the clue; and in the third, which, objectively, apes myelogenous leukemia, there is an aleukemic blood picture. The aleukemic state of the blood in cases of *lymphatic hyperplasia* and of *splenic* and *renal tumors* is a sure criterion in distinguishing such lesions from leukemia.

Here may be mentioned the remarkable effect of the Röntgen-ray in the treatment of myelogenous leukemia. The disappearance of the myelemia and of the splenomegaly thus effected is, unfortunately, believed to mirror a symptomatic improvement and not a radical cure of the disease. I have found that röntgenization of the tibial and femoral marrow produces much more rapid and certain results than the exposure of the splenic area to the rays, as is ordinarily practised. Energetic treatment with arsenic alone sometimes causes similar results. The reader should consult Dock's monograph [30] and the articles by Brown and Jack [31] and by Heineke [32] for full data concerning this subject.

Hodgkin's Disease.—Here the blood shows merely a variable grade of anemia, with a normal leukocyte count, or, very rarely, a moderate leukocytosis. These negative findings distinguish Hodgkin's disease from *leukemia,* its clinical counterfeit, but they are no criterion in differentiating other forms of adenoid overgrowth which may be accompanied by identical blood changes.

Splenic Anemia.—Well-defined anemia with leukopenia and relative

lymphocytosis is the quite uncharacteristic blood finding in this uncertain clinical entity. Of the several conditions which may be confused with splenic anemia, *myelogenous leukemia* is distinguished by its distinctive myelemia; *pernicious anemia*, by its megaloblastic blood picture; *ague cake*, by the presence of the malarial parasite, or, at least, of pigment; *echinococcus* of the spleen, by eosinophilia; and *malignant disease* of the spleen, by leukocytosis.

Secondary Anemia.—The degree of a symptomatic anemia ranges from a trivial hemoglobin deficiency to a grade of blood impoverishment so striking as to masquerade as true pernicious anemia. The average case, however, shows a well-marked though not excessive hemoglobin and erythrocyte loss, with corresponding evidences of cellular degeneration. The color index is more likely to be moderately subnormal than either extremely high or low. Nucleated erythrocytes, especially normoblasts, occur in severe cases. Moderate leukocytosis, usually due to complications, is found in many instances, and the plaques are generally more numerous than in normal blood.

The following data, based upon 200 consecutive blood examinations, show the average blood changes in different anemias:

Form of Anemia.	Hemoglobin Loss.	Erythrocyte Loss.
Secondary Anemia	44.8 per cent.	27.1 per cent.
Chlorosis	54.8 " "	17.8 " "
Pernicious Anemia	74.5 " "	76.9 " "
Leukemia	60.6 " "	45.4 " "

The special features of the blood in the secondary anemias and the clinical applications of such findings are discussed in Part IV. (See p. 131, *et seq.*)

Alterations in the Blood Volume.—*True plethora* is an increase, cellular and fluid, in the volume of the blood, such as may result temporarily from the transfusion of blood or from forcing into the general circulation the blood of a part to be severed from the body, as by the use of an Esmarch bandage before an amputation. The habitual polyemia of the so-called "plethoric" individual is but conjectural. *Serous plethora* is an increase in the blood volume due to an excess of plasma, attributable to such causes as low vasomotor tension, cardiac failure, and the introduction of an undue amount of fluid by ingestion or by injection. *Cellular plethora*, or polycythemia, is characterized by an increase in the hemoglobin percentage and in the erythrocyte count in excess of the normal standard; it is a relative rather than an absolute condition. (See p. 121.) *Hydremia*, or dilution of the blood, involves simply a relative plasma increase without an increase in the total volume of blood; it may arise from the causes of serous plethora, and also occurs in anemia, in dropsy, and after hemorrhage. *Anhydremia* is a concentration of the blood, dependent upon a loss of plasma, of which change increased arterial tension and sudden, large drains upon the body-fluids are active factors. Dilution and concentration of the blood are of practical interest in the interpretation of the blood report, since in the former condition perfectly normal blood may appear anemic, while in the latter anemic blood may seem normal.

Lipemia.—When the blood contains fat in excess (3.25 parts per thousand being the maximum normal amount), the condition is known as *lipemia*. Physiologically, lipemia occurs during digestion, in the nursling, in obesity, in pregnancy, and as the result of menstrual suppression. Pathologically, it is found in a great variety of lesions, of which the most important are diabetes mellitus, gout, arteriosclerosis, and many of the acute fevers. Fractures involving injury of the fatty marrow and lacerated wounds of blood-vessels traversing fatty tissues also may excite lipemia, which occasionally is so excessive that fatal fat embolism results.[33] *Lipacidemia*, or the presence of volatile fatty acids in the blood, has been noted in diabetes mellitus, in leukemia, and in various pyrexias; in fevers the blood may also contain an appreciable amount of acetone —*acetonemia*.

Glycemia.—When the normal sugar content of the blood, 1 to 1.5 pro mille, is exceeded, the condition is termed *hyperglycemia*. This change is encountered in diabetes mellitus, in carcinoma, in some of the acute infections, after splenectomy, and after ligation of the pancreatic duct. The presence of hyperglycemia in carcinoma and its absence in sarcoma have been emphasized by Freund[34] and by Trinkler[35] as a differential point between these two forms of neoplasm. *Williamson's test*,[36] which consists in the decolorization of an alkaline solution of methylene-blue by diabetic blood, has proved dependable in my hands. *Bremer's test*,[37] or the atypical staining affinities of diabetic blood, is not specific, since similar peculiarities have been noted in non-diabetic bloods.

Other pathologic changes affecting the whole blood include *cholemia*, or the impregnation of the blood with bile or bile pigments which occurs in conditions of icterus; *uricacidemia*, or the presence in the blood of a demonstrable quantity of uric acid, as in gout, leukemia, pneumonia, and a number of other diseases; and *melanemia*, or the occurrence of pigment in the blood—a familiar finding in the malarial fevers, and an occasional one in melanotic sarcoma, in Addison's disease, and in insolation.

Parasitology of the Blood.—**Bacteriemia.**—The demonstration that most of the specific infections are in reality bacteriemias is due to the recent perfection of the technic of blood culturing, a method of research which today furnishes accurate, final information in many obscure diseases. The bacillus of Eberth, for instance, can be cultivated from the blood in about 80 per cent. of all cases of *enteric fever*, the highest percentage of positive findings occurring during the first week of the infection, generally before the appearance of the serum reaction. In *paratyphoid fever* similar results with the paratyphoid organism have also been obtained. In the identification of many puzzling septic conditions bacteriologic examination of the blood frequently gives just the sought-for clue; this is conspicuously true of *malignant endocarditis*, *pneumococcus infection*, *gonorrheal sepsis*, *bubonic plague*, *acute tuberculosis*, *glanders*, *cerebrospinal fever*, and *septic states* of cryptogenic character. The presence of streptococci in the blood in many cases of *scarlatina* and of *rheumatic fever* has also been reported. In *anthrax*, *influenza*, and *Malta fever* the specific

bacteria are found in the circulating blood only in exceptional instances.

Hematozoa.—Microscopic examination of the fresh and stained film of finger-blood is resorted to in seaching for the *Hæmamœba malariæ*, the *Spirillum Obermeieri*, the *Filaria sanguinis hominis*, the *Trypanosoma gambiense*, and the *Treponema pallidum*. The *Leishman-Donovan body* of tropical splenomegaly is usually obtained by splenic puncture, since it appears in the general circulation only in rare instances. It may here be noted that the specificity of the so-called *Piroplasma hominis* of Montana spotted fever has not been conclusively proved.

Other blood parasites, not invading the general blood-stream, are the *Bilharzia hematobia*, residing in the portal vein and its branches, and, very rarely, in the pulmonary circulation; and the newly discovered fluke, the *Schistoma cattoi*, inhabiting the capillaries of the intestines, the liver, and other parts of the alimentary canal.

III. THE CELLULAR ELEMENTS OF THE BLOOD.

The Erythrocytes.—The *erythrocytes* or *red corpuscles* are smooth, elastic, non-nucleated biconcave discs, about 7.5 μ* in diameter, and consisting of a spongy network (*the stroma of Rollet*) in the meshes of which the hemoglobin is embedded. In normal blood the erythrocytes tend to collect and adhere like rolls of coins stacked up face to face, this being known as *rouleaux formation*. A loss of this tendency (*hypoviscosity*) occurs in severe anemia, and an exaggeration of the cells' adhesive properties (*hyperviscosity*) is met with in many of the acute infections and as the result of the toxic action of certain blood poisons.

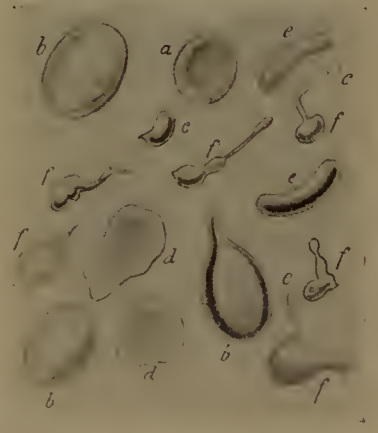


Fig. 26.—Deformities of Size and Shape of the Erythrocytes.

a, Normal erythrocyte; *b*, megalocytes; *c*, microcytes; *d*, hemoglobin-deficient erythrocytes; *e*, sausage-shaped poikilocytes; *f*, common types of poikilocytes.

The *normal number* of erythrocytes is approximately 5,000,000 per cubic millimeter in the man; 4,500,000 in the woman; and from 6,000,000 to 7,000,000 in the newly born infant. The *volume index*, indicating the percentage volume of the individual cell, is normally 1.00; it roughly parallels the color-index, falling notably in chlorosis, declining moderately in leukemia and in the secondary anemias, and rising above normal in true pernicious anemia. *Polycythemia*, or an increase in the number of erythrocytes above the normal standard, may be due to physiologic and to pathologic factors. Physiologically, an increase of this sort occurs during digestion, and from the effects of active muscular exercise, massage, cold or hot tubbing, and fasting. Normal pregnancy, lactation,

*The Greek μ (micromillimeter) stands for $\frac{1}{1000}$ mm. in microscopy.

and menstruation cause little or no numerical changes in the cells. Pathologically, polycythemia is referable to many different causes, mainly those which concentrate the blood either by draining off its liquids or by provoking peripheral stasis. Thus, abnormally high erythrocyte counts develop during residence in high altitudes; as the result of active purging, emesis, and sweating; during the reformation of an exudate following paracentesis; from the effects of cyanosis, as in Osler's disease, valvular cardiac lesions, pulmonary diseases, and asphyxia; and after blood transfusion and during active hemogenesis. The number of cells is also greater than normal in many cases of incipient phthisis, acute yellow atrophy of the liver, myxedema, diabetes mellitus, bubonic plague, severe burns, insolation, and poisoning by phosphorus and by illuminating gas.

Oligocythemia, or a diminution in the number of erythrocytes, is symptomatic of some form of anemia, and is accompanied by more or less hemoglobin loss or oligochromemia, and perhaps occasionally by a reduction in the blood volume or oligemia.

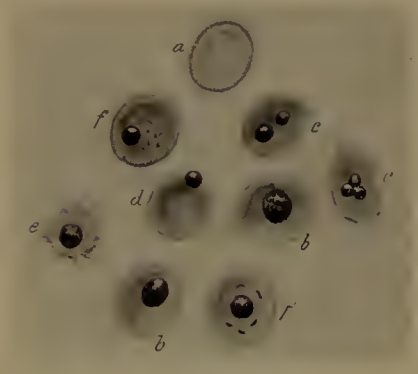


FIG. 27.—TYPES OF THE NORMOBLAST.

a, Normal erythrocyte; *b*, common types of the normoblast; *c*, normoblasts containing multiple (divided) nuclei; *d*, normoblast showing apparent nuclear extrusion; *e*, microblast; *f*, normoblasts showing granular basophilia.

Pathologic Structural Changes.—*Deformities of Size and Shape.*—Changes affecting the size and the shape of the erythrocytes occur in all severe anemias, the degree of such alterations corresponding to the grade of the anemia of which they are symptomatic. These abnormalities are due to some form of defective hemogenesis, owing to which faultily formed and peculiarly vulnerable cells are bred in the bone-marrow, and thence reach the general circulation. Abnormally large-sized cells are known as *megalocytes* (Fig. 26), and the prevalence of such cells (*megalocytosis*) is the rule in severe types of anemia, especially in the pernicious form, of which a general increase in the erythrocytes' diameter is a clinical hallmark. Unduly small-sized erythrocytes are termed *microcytes* (Fig. 26), and their presence in large numbers (*microcytosis*) is a common finding in chlorosis and in well-marked secondary forms of anemia. *Poikilocytes* (Fig. 26) are misshapen erythrocytes of various sizes and of differing grades of deformity; such cells, while not distinctive of any specific kind of anemia, are especially numerous (*poikilocytosis*) in pernicious anemia and in leukemia. The above varieties of cell deformity generally coexist in conditions of blood impoverishment, and the general rule holds true that the milder anemias cause moderate microcytosis and small-celled poikilocytosis, and that the severer forms excite extreme megalocytosis and large-celled poikilocytosis.

The foregoing changes are closely associated with *endoglobular necrosis* of the cells which results in their dehemoglobinization, and with *total cell necrosis*, which is an extreme type of structural decay ending in fragmentation or *schistocytosis*.

Erythroblasts.—Nucleated erythrocytes or erythroblasts are of two distinct varieties, normoblasts and megaloblasts, each of which differs not only histologically, but also in origin and in clinical significance. The typical *normoblast* (Plate I; also Fig. 27) is a cell the size of the normal erythrocyte (normocyte), and is provided with a relatively small spherical nucleus which stains deeply with the basic anilin dyes; in some forms the nucleus is apparently extruded from the cell-body, in others it is convoluted or actually divided, and in still others it is of large size and of a feebly basic tendency, these last peculiarities betraying extreme histologic youth. The cell-stroma usually resembles that of the normocyte. The *megaloblast* (Plate I; also Fig. 28) is a large-sized cell, and its nucleus, which is very feebly basic, occupies the greater part of the cell-body; in atypical forms the nucleus is twisted, indented, or divided, and deeply stained, this peculiarity being a sign of extreme senility. The cell-body is often swollen, irregular, and marked by stigmata of degeneration. (See below.) The *microblast* is a small nucleated erythrocyte, consisting of a spherical basic nucleus encircled by a narrow ragged rim of cell-body. This cell is regarded as a normoblast dwarfed by the degeneration and solution of its protoplasm.

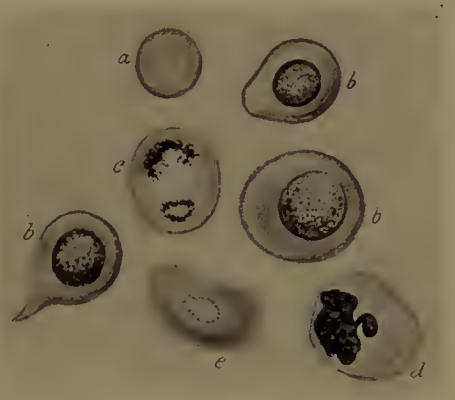


FIG. 28.—TYPES OF THE MEGALOBLAST.
a, Normal erythrocyte; *b*, common types of the megaloblast; *c*, megaloblast showing nuclear division (karyokinesis); *d*, megaloblast showing nuclear solution (karyolysis); *e*, erythrocyte containing a ring body.

The presence in the blood of any form of nucleated erythrocyte indicates an intense anemia, and the adequacy of the bone-marrow in compensating the blood loss is shown by the prevailing type of such cells. Normoblasts, bred in normal marrow, stand for active, adult hemogenesis, and are the prevailing erythroblast found in anemias with active regeneration of the blood, such as chlorosis, post-hemorrhagic and other favorable secondary anemias; megaloblasts, originating in fetal marrow, betray sluggish, embryonic hemogenesis, and are the predominating nucleated cell in pernicious anemia, in which embryonic reversion of the marrow exists. The gravity, then, of an anemia is reflected by the relative abundance of these two opposite types of erythroblasts, since the normoblast expresses regeneration, and the megaloblast degeneration, of the hematopoietic functions.

Polychromatophilia and Granular Basophilia.—The normal erythrocyte, when stained with a mixture of acid and basic dyes, shows a selective affinity for the acid dye, but the pathologic erythrocyte loses this affinity and is stained irregularly by both acid and basic elements, thus exhibiting *polychromatophilia* or *anemic degeneration*, a change whose intensity is gaged by the cell's capacity for the basic stain. Polychromatophilia is distinctive of no special type of anemia, but it is particularly well marked

in pernicious anemia and in the leukemias. *Granular basophilia* is a peculiar basic stippling, fine or coarse, of the stroma of the erythrocyte, best brought out with eosin-methylene-blue mixtures. It is probably a sign of stroma degeneration, affects both erythrocytes and erythroblasts, and is frequently associated with polychromatophilia. Basophilic cells may be found in many forms of severe anemia, but they are especially common in lead poisoning, in pernicious anemia and leukemia, and in the anemias secondary to sepsis, malignant disease, and the acute infections.

Ring Bodies.—Ring-shaped bodies within the erythrocytes and similar extracellular figures, staining both metachromatically and basically, have been described by Cabot[38] and by Strauss and Rohnstein.[39] They closely resemble the nuclear outlines of erythroblasts and suggest nuclear remnants. Cabot has found such ring-bodies in lead poisoning, in leukemia, and in pernicious anemia, and I have also noted them in the latter disease, as well as in the anemia of grave sepsis. A special form of stroma degeneration known as *Schüffner's granules* is met with in tertian malarial fever, and consists of a coarse red stippling of the parasitiferous erythrocytes in specimens stained with polychrome methylene-blue.

The Leukocytes.—The *leukocytes* or *white corpuscles* are nucleated colorless cells, most of which are of larger size than the erythrocytes, by which they are outnumbered approximately seven-hundredfold. They appear as irregular spheroidal bodies consisting of a nuclear mass and a protoplasmic body which in some of the cells is quite hyaline and in others crowded with delicate granules. In the adult the *normal number* of leukocytes ranges between 5,000 and 10,000 per cubic millimeter of blood, and averages about 7,500; in the young infant a count of 20,000 or 30,000 is physiologic. Details relating to phagocytosis, pinocytosis, opsonic action, and other phases of the leukocyte function are dealt with elsewhere. (See p. 174.)

Varieties of Leukocytes.—The different varieties of leukocytes are identified microscopically both by their morphology and by the technic of "color analysis," first proposed by Ehrlich.[40] By this method the various structures of the cells—nucleus, protoplasm, and granules—are selectively colored by staining a dry, fixed blood film with the acid, basic, and neutral anilin dyes, so that their distinctive characteristics may be readily distinguished. In a specimen of normal blood thus stained the following types of leukocytes are demonstrable:

Variety of Cell.	Relative Percentage.	Absolute Number Per Cubic Millimeter of Blood.
Small lymphocytes	20 to 30	1,000 to 3,000
Large lymphocytes and transitional forms	4 to 8	200 to 800
Polynuclear neutrophiles	60 to 75	3,000 to 7,500
Eosinophiles	.5 to 5	25 to 500
Basophiles	.5	25

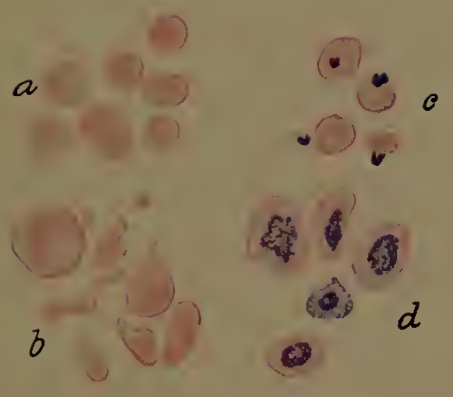
In addition to these six normal varieties of leukocytes, there are three pathologic types which are found in the blood only as the result of some hematopoietic disturbance. These cells are the *myelocytes*, the *mast cells*, and the so-called *stimulation forms*.

PLATE I.

NORMAL AND PATHOLOGIC FORMS OF BLOOD-CORPUSCLES.

1. Normal, Deformed, and Nucleated Erythrocytes. (Wright's Stain.)
   a, Normal erythrocytes; *b*, Deformities of size and shape; *c*, Normoblasts; *d*, Megaloblasts.
2. Granular Basophilia and Polychromatophilia of the Erythrocytes. (Wright's Stain.)
   a, Normal erythrocytes; *b*, Granular basophilia; *c*, Polychromatophilia.
3. Normal and Pathologic Types of Leukocytes. (Wright's Stain.)
   a, Small lymphocytes; *b*, Large lymphocytes; *c*, Transitional form; *d*, Polynuclear neutrophiles; *e*, Polynuclear eosinophiles; *f*, Eosinophilic myelocyte; *g*, Mast cells; *h*, Neutrophilic myelocytes; *i*, Blood plaques.
4. Iodophilia. (Goldburger-Weiss Stain.)
   A. Normal Blood.
   B. Blood from a Case of Sepsis.
   a, Granular type of reaction (intracellular); *b*, Diffuse type of reaction (intracellular); *c*, Extracellular iodophilic mass.

PLATE I.



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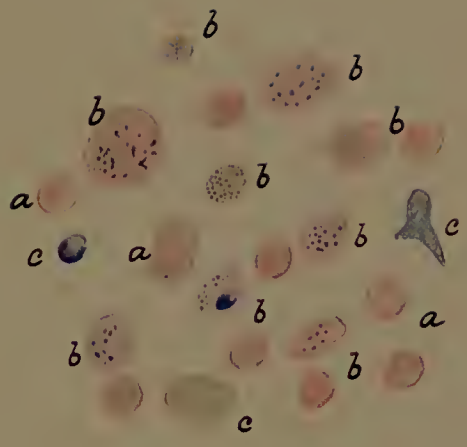

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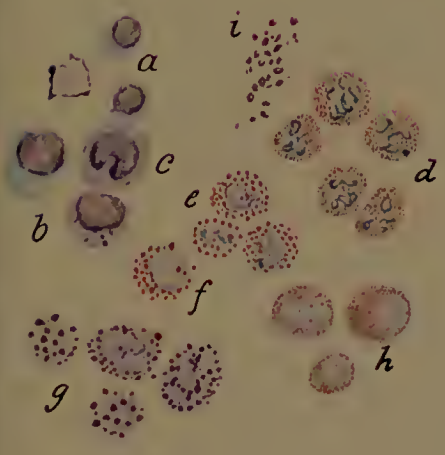

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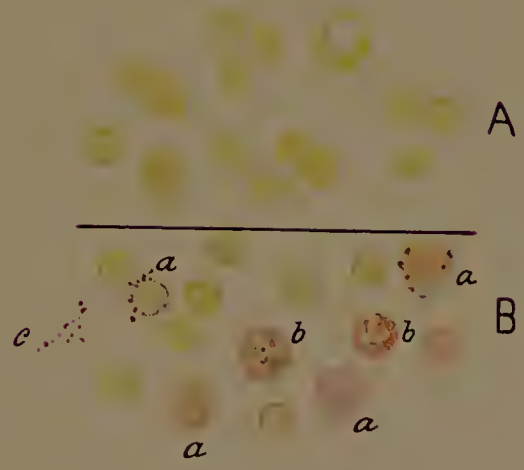

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Lymphocytes.—The small lymphocyte (Plate I, Fig. 3) is a cell about 7.5 μ in diameter, and consists of a spherical nucleus (rarely lobulated or divided) encircled by a narrow rim of protoplasm. Both the nucleus and the protoplasm are intensely basic, the latter usually the more so. The large lymphocyte (Plate I, Fig. 3), which is 10 μ or more in diameter, does not differ materially from the small form, save in size. Both types of lymphocytes are natives of lymphoid tissue, and are classed as nongranular cells, although exceptionally their protoplasm contains a few coarse metachromatic granulations. With these cells may be classed the so-called large mononuclear leukocyte, probably marrow-bred, and differing chiefly from the true lymphocyte in having a very slight basic affinity, especially of the protoplasm, which stains less deeply than the nucleus.

Transitional Forms.—This type of cell (Plate I, Fig. 3) resembles the large lymphocyte in size, but its nucleus is more basic, and indented, reniform, or crescentic in shape. The protoplasm is faintly basic and contains no actual granules. The clinical significance of the transitional cell is the same as that of the large lymphocyte.

Polynuclear Neutrophiles.—The polynuclear neutrophile (polymorphonuclear neutrophile; finely granular oxyphile) is a spherical or ovoid leukocyte 10 or 12 μ in diameter (Plate I, Fig. 3), with a single, twisted, lobulated nucleus of basic affinity (rarely with multiple nuclei), and a protoplasm densely crowded with fine neutrophile granules. These are the ε-granules of Ehrlich, which, though described as of "neutral" affinity, in reality have a faintly acid tendency.

Polynuclear Eosinophiles.—(Polymorphonuclear eosinophile; coarsely granular oxyphile.) This is a cell like the polynuclear neutrophile in size and general morphology, but differing in that the nucleus is less convoluted and less basic, and in that the protoplasm is studded with coarse eosinophile granules—hence the term "eosinophile," by which abbreviation this cell is commonly designated (Plate I, Fig. 3). The eosinophile or α-granules are intensely stained by an acid dye, such as eosin.

Polynuclear Basophiles.—But for the presence of delicate basic protoplasm granules and a distinctly less basic nucleus, this cell counterfeits in size and shape the polynuclear neutrophile (Plate I, Fig. 2). The granules, which stain with a basic dye, such as methylene-blue, are also known as δ-granules.

Myelocytes.—Of this pathologic variety of leukocyte (Plate I, Fig. 3) there are two types, the neutrophilic and the eosinophilic, the former being much the commoner. Each of these types of the myelocyte is from 10 to 20 μ in diameter, or even larger, and each has a relatively large nucleus which is usually of spherical contour, but sometimes is notched, constricted, or quite divided. The distinguishing feature of these cells is the granules embedded in their protoplasm, the neutrophilic myelocyte containing fine neutrophile granules, and the eosinophilic myelocyte, coarse eosinophile granules.

Mast Cells.—The mast cell (Plate I, Fig. 3) consists of a delicate spherical or ovoid nucleus surrounded by a mass of γ-granules which show

an intensely metachromatic affinity, and vary in size from the finest stippling to a coarse cube. The nucleus, being almost structureless, shows scarcely any affinity for basic dyes, and the protoplasm is even more indefinable, so that the cell may appear simply as a collection of granules molded into a round mass varying in diameter from a minimum of 7 or 8 μ to a maximum of 20 μ.

Stimulation Forms (*Reizungsformen*).—These are cells of from 5 to 15 μ in diameter, with a single round basic nucleus of relatively small size and a non-granular protoplasm of a modified basic tendency. The exact significance of these stimulation forms is obscure, but they are known to invade the blood stream in association with the myelocytes.

Leukocytosis.—(Plate II, Fig. 1.) Leukocytosis is an increase above normal in the number of leukocytes in the peripheral blood, usually involving the polynuclear neutrophiles both absolutely and relatively, but exceptionally affecting all types of cells proportionately.* Thus, the criterion of a leukocytosis is not simply the *total number* of cells, but the *variety*, which accounts chiefly for the gain. To say that a blood-count shows 50,000 leukocytes per cubic millimeter may mean either leukocytosis or leukemia, but to add that 90 per cent. of this fivefold increase are polynuclear neutrophiles unquestionably means a true leukocytosis. Merely a relatively high percentage of polynuclear neutrophiles cannot be interpreted as a frank leukocytosis, as some writers profess to believe, upon wholly insufficient grounds.

Physiologic Leukocytosis.—Leukocytosis, usually of moderate degree and of brief duration, may depend upon numerous physiologic factors, the change here being attributable mainly to blood concentration and to peripheral stasis, rather than to stimulation of the hematopoietic organs. Increases due to such causes occur in the newly born, during digestion, during pregnancy and parturition, as a pre-agonal sign, and from various mechanical and thermal influences. The fact that causes such as these may account for a leukocytosis is always to be recalled in reading the blood report in a clinical light.

Pathologic Leukocytosis.—Leukocytosis is commonly associated with many pathologic states, chiefly those of infectious, inflammatory, and toxic natures, and in such instances the change reflects an overproduction of cells by the bone-marrow, in order thus to fortify the organism's defensive powers against disease. How this is accomplished has already been described in the chapter on Immunity (*q. v.*). The stage of actual leukocytosis (or *hyperleukocytosis*) is preceded by a brief period of diminution in the number of cells (or *hypoleukocytosis*), due to the initial shock of the irritant.

In disease the behavior of the leukocytes is an index to the intensity of the morbid irritant and to the individual's resisting powers. Regarded in this light and correlated with other clinical data, the leukocyte count often proves of the greatest practical value, but its interpretation as a pathogno-

* The term leukocytosis, as applied to a leukocyte increase regardless of the kind of cells involved, is perfectly justified by etymology, but usage and simplicity should restrict its use to a cellular increase affecting chiefly the polynuclear neutrophiles.

monic sign, to the exclusion of the bedside symptoms, courts diagnostic disaster and sows the seed of hematologic skepticism. No qualified clinician cares to divorce the laboratory from the ward.

Clinically, it is convenient to consider pathologic leukocytoses etiologically, under these subheadings: (I) Inflammatory and infectious leukocytosis; (II) Post-hemorrhagic leukocytosis; (III) The leukocytosis of malignant disease; and (IV) Toxic leukocytosis. The leukocytoses experimentally provoked by the use of various chemicals, bacterial products, organic principles, and surface revulsives are of purely scientific interest.

I. Inflammatory and Infectious Leukocytosis.—Here are included the leukocytoses symptomatic of inflammatory and infectious conditions, of which abscess, sepsis, pneumonia, and scarlet fever are types. In such instances the behavior of the leukocytes is determined by these fundamental facts: (1) That infection or irritation of the human organism provokes a compensatory hyperactivity of the bone-marrow, whereby this tissue is stimulated to the overproduction and output of leukocytes, especially of the polynuclear neutrophile type, which, as disease-repelling elements, flood the blood-stream. (2) That the peripheral leukocyte count reflects the activity of this marrow reaction, which may be excessively stimulated, moderately excited, or entirely overwhelmed and stifled, according to the virulence of the irritant and the vital forces of the subject. In general terms, it is true that serous exudates are accompanied by less of a leukocyte reaction than purulent, and that acute disseminated inflammations excite higher counts than chronic circumscribed lesions. Fever *per se* is wholly without influence.

The following table serves to illustrate the leukocyte range in relation to the intensity of the irritant and the reaction offered by the individual.

Degree of Leukocytosis.	Intensity of Irritant.	Resisting Powers.
Marked.	Marked.	Normal.
Slight.	Moderate.	Normal.
Slight.	Moderate.	Indifferent.
Absent.	Marked.	Feeble.
Absent.	Feeble.	Normal.

The most important factors of true inflammatory and infectious leukocytoses are tabulated herewith:

I. *General Infections.*

Asiatic cholera.	Malignant jaundice.	Spotted (Montana) fever.
Bubonic plague.	Pneumonia.	Tetanus.
Cerebrospinal fever.	Relapsing fever.	Trichiniasis.
Diphtheria.	Rheumatic fever.	Typhus fever.
Dysentery.	Scarlet fever.	Vaccinia.
Filariasis.	Secondary syphilis.	Varicella.
Glanders.	Septicemia and pyemia.	Variola.

II. *Local Lesions.*

Acute nephritis.	Arthritis.	Cholangitis.
Actinomycosis.	Bronchitis.	Cholecystitis.
Appendicitis.	Burns.	Dermatitis.

Endocarditis.	Hydatid disease.	Pancreatitis.
Enteritis.	Infected wounds.	Pericarditis.
Erysipelas.	Mastitis.	Peritonitis.
Gangrene.	Meningitis.	Purulent lesions.
Gastritis.	Multiple neuritis.	Splenitis.
Hanot's cirrhosis.	Osteomyelitis.	

Post-operative leukocytosis, symptomatic of a reaction excited by the normal process of wound repair, follows surgical operations, and causes a moderate cell increase which develops immediately after the operation, attains a maximum usually within twenty-four hours, and disappears within from two to four days. A persistent leukocytosis beyond this period suggests infection, defective drainage, spreading inflammation, or hemorrhage. The influence of the anesthetic, the effect of hemorrhage, and the surgical cleanliness of the wound are side-lights always to be thrown upon the figures of a post-operative leukocyte count.

In contrast to the above-named factors of leukocytosis, there is also an important group of specific infections in which leukocytosis never occurs, except as the result of some complication. The diseases of which this is true are mentioned elsewhere. (See "Leukopenia," p. 129.)

II. Post-hemorrhagic Leukocytosis.—An acute, well-marked hemorrhage promptly excites a leukocytosis, usually distinguishable within a few hours after the blood loss and lasting for three or four days, in the average case. In fatal cases, however, the count may never exceed normal, or the increase may be so short-lived as to escape detection. Trauma, venesection, post-partum hemorrhage, and the rupture of an aneurism typify the exciting causes of this variety of leukocytosis. As a rule, little or no increase attends chronic hemorrhages—the hemoptysis of phthisis, the hematemesis of gastric cancer or ulcer, the oozing uterine fibroid, and bleeding piles rarely raise the count, probably because these moderate blood losses plus the individual's tolerance negative marrow reaction.

III. Leukocytosis of Malignant Disease.—The leukocytoses occurring in sarcoma and in carcinoma are due less to any specific toxicity than to coexisting infections and inflammations. In my experience about one-half of all cases of malignant disease show frank leukocytosis, and in all but about five per cent. the count is moderate. The change is likely to be most striking in large visceral growths with metastases, and least marked in small, superficial, local tumors. A further discussion of the blood findings in malignant neoplasms will be found in a subsequent section. (See p. 138.)

IV. Toxic Leukocytosis.—Here a non-bacterial toxic irritant causes the increase, the degree and persistence of which are explained by the theories applicable to infectious leukocytoses. The count is high in acute poisoning by ammonia, corrosive metallic salts, nitrites, alcohol, acetanilid, phosphorus, potassium chlorate, tansy, toluylendiamin, ptomains, carbon monoxid, and snake venom; in toxic forms of delirium and convulsions, *i. e.*, uremia, cholemia, and epilepsy; and in narcosis by ether and by chloroform.

Leukopenia.—A subnormal number of leukocytes in the peripheral blood is termed *leukopenia* or *hypoleukocytosis*. A physiologic type of

PLATE II.

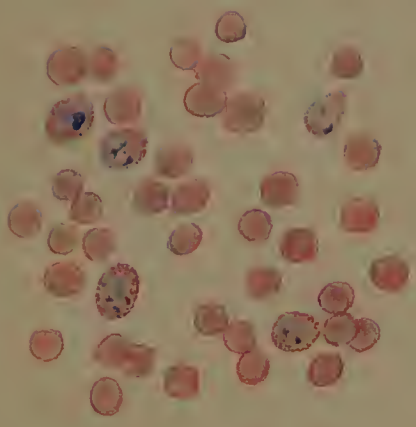

FIG. 1.—LEUKOCYTOSIS.

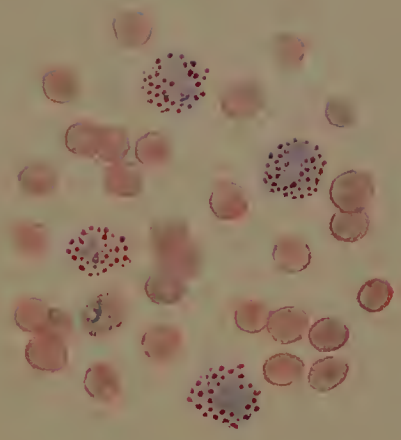

FIG. 2.—EOSINOPHILIA.

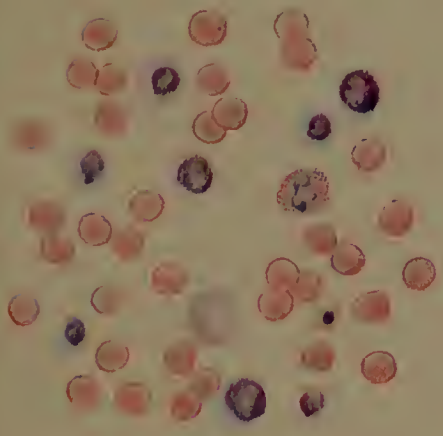

FIG. 3.—LYMPHATIC LEUKEMIA.

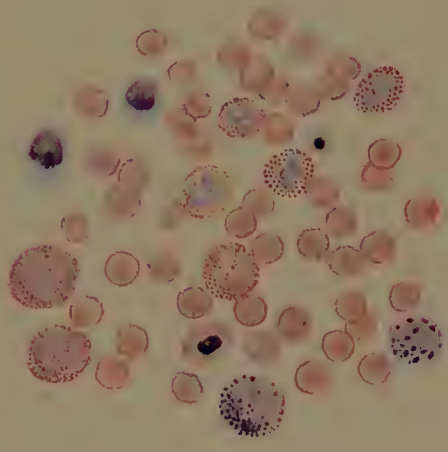

FIG. 4.—MYELOGENOUS LEUKEMIA.

(Wright's stain.)

leukopenia, depending upon a peripheral poverty of leukocytes due to vasomotor disturbances, is provoked by brief hot, and by prolonged cold, baths, by sensory nerve stimulation, and by lowered blood-pressure. Starvation and other conditions of malassimilation also are attended by a low leukocyte count.

The clinical significance of leukopenia in acute infections which ordinarily cause leukocytosis has already been described. In the following group of diseases, mainly infectious, leukopenia, or at least no leukocytosis, is the rule, save in the event of complications:

Chlorosis.	Measles.
Enteric fever.	Paratyphoid fever.
Hodgkin's disease.	Peptic ulcer.
Influenza.	Pernicious anemia.
Kala-azar.	Rötheln.
Laennec's cirrhosis.	Splenic anemia.
Leprosy.	Sprue.
Malarial fever.	Trypanosomiasis.
Malta fever.	Tuberculosis.

Experimentally, leukopenia may be induced by the administration of various anticoagulant substances and other agencies, chemical and organic, which destroy the cells. Rapid destruction of the leukocytes has been noted in animals exposed to the action of the Röntgen[41] rays, and the same thing occurs in leukemic persons thus treated. Neither radium rays nor ultraviolet light has any effect upon the leukocytes or the other elements of the blood.

Lymphocytosis.—(Plate II, Fig. 3.) Increase in the number of lymphocytes of the peripheral blood is termed lymphocytosis, a change which may be either relative, *i. e.*, due to a high percentage of lymphocytes without leukocytosis; or absolute, with both the lymphocytes and the total leukocyte count increased. Lymphocytosis is best accounted for by an activity of the lymphatic tissues, and by unequal distribution of the cells throughout the circulation.

Absolute lymphocytosis (lymphemia) is the blood picture of lymphatic leukemia, chloroma, pertussis, variola, and certain cases of infantile pneumonia. *Relative lymphocytosis* is a striking differential change in enteric, malarial, and Malta fevers; in trypanosomiasis, kala-azar, and other types of tropical splenomegaly; in tuberculosis, syphilis, rickets, scurvy, scrofula, and lymphosarcoma; and in some of the primary anemias. It also occurs after hemorrhage, after splenectomy, and as a pre-agonal sign. Relatively high lymphocyte figures are to be looked for in young children and in cachectic, debilitated conditions. It is generally true that diseases characterized by leukopenia also involve a relative lymphocyte gain, which being referable simply to diminution in the polynuclear neutrophiles, is really a fictitious change.

Eosinophilia.—(Plate II, Fig. 2.) This term means an increase in the number of eosinophiles in the circulating blood, and is due to the specific, selective action of a chemotactic irritant upon the eosinophil-

ous marrow cells. With great constancy eosinophilia is found in helminthiasis, especially in trichiniasis, hydatid infection, filariasis, and intestinal worms; in various dermatoses; in diseases of the bones; in syphilis, bronchial asthma, chylous effusions, and myelogenous leukemia; and during the postfebrile period of acute pyrexias. A compensatory eosinophilia develops after splenectomy and in many lesions of the spleen. For a list of numerous other (reputed) factors of eosinophilia text-books on hematology should be consulted.

Subnormal eosinophile estimates are common in lymphatic leukemia, chlorosis, pernicious anemia, and tuberculosis; during the active pyrexia of most infections; after large hemorrhages; and as a pre-agonal blood change.

Myelemia.—The presence of myelocytes in the circulating blood, always a pathologic sign, is termed *myelemia* or *myelocytosis*. (Plate II, Fig. 4.) Myelemia, plus leukocytosis, is especially constant in myelogenous leukemia, in von Jaksch's multiple periostitis, and in malignant disease with bone metastases. Less commonly, the blood contains small numbers of myelocytes in the severer types of other anemias, both primary and secondary, and in those conditions associated with active leukocytosis. A trifling myelemia with marked anemia suggests a crippling of the marrow's hemogenetic functions, by fault of which imperfect, undeveloped polynuclear neutrophiles, of which myelocytes are the immediate ancestors, are to some extent produced; a striking myelemia with leukocytosis indicates that the marrow is so overstimulated in its endeavor to meet the call for polynuclear neutrophiles that these young myelocytic cells prematurely flood the general circulation. Both forms of neutrophiles, polynuclear and myelocytic, are believed to respond to identical chemotactic irritants. Similarly, the same irritants stimulate polynuclear eosinophiles and eosinophilic myelocytes, their parent cells.

Basophilia.—(Plate I, Fig. 2.) This word is applicable to an increase of the basophilic leukocytes in the blood-stream, a sign invariably to be regarded as pathologic and to be interpreted as the effect of a specific type of marrow stimulation. Enormous mast cell basophilia occurs in myelogenous leukemia, and a very moderate increase in many of the helminthiases, in Asiatic cholera, in the cachectic anemias, and in numerous dermatoses. I have found abnormally high mast cell figures in the primary anemias; in plumbism and Hanot's cirrhosis; and in actinomycosis, trichiniasis, filariasis, echinococciasis, and trypanosomiasis.

Iodophilia.—(Plate I, Fig. 4.) In numerous morbid states the dried blood film, when treated with iodin, shows many iodophile leukocytes or cells exhibiting an affinity for iodin. In such cells, generally polynuclear neutrophiles, the protoplasm is colored diffuse mahogany-brown or it contains discrete reddish-brown granules, while extracellular iodophile masses (possibly disintegrated leukocytes) also are observed. In an iodin-stained specimen of normal blood the leukocytes' protoplasm is tinged a pale lemon shade and their nuclei are colorless.

Iodophilia means simply toxemia, either bacterial or chemical, and probably denotes a form of leukocyte degeneration. It is a corollary of

leukocytosis, and, like the latter, should be considered as symptomatic and not as pathognomonic. It is even more trustworthy than leukocytosis as a sign of infection, for grave toxemias which stifle leukocyte increases serve only to intensify iodophilia. Iodophile leukocytes occur in all purulent lesions attended with pus absorption, but they are absent in walled-off abscess. They are also present with great constancy in cryptogenic sepsis, pneumonia, and other infections; and in malignant disease, grave anemias, and severe cachexias. In enteric fever iodophilia may point to either intense infection or to hemorrhage, perforation, or other accident. In pure tuberculosis the reaction is negative. From a clinical standpoint, iodophilia suggests septic not tuberculous abscess, purulent not catarrhal appendicitis, septic not rheumatic nor tuberculous arthritis, malignant not benign tumor. Persistent iodophilia after the incision of an abscess indicates imperfect drainage; and after a pneumonic crisis, delayed resolution or some other post-critical complication.

Blood-plaques.—(Plate I, Fig. 3.) The blood-plaques or platelets are non-nucleated globular bodies, which tend to adhere in the plasma in racemose groups. They measure 1 to 4 μ in diameter, and are of amphophilic affinity, of quite obscure origin, and of wide normal numeric range—200,000 to 500,000 per cubic millimeter of blood, or even higher. Of their clinical significance little is known save that they are diminished in most of the acute fevers, in the hemorrhagic diatheses, in pernicious anemia, and in severe burns; and that they are commonly very numerous in many high-grade anemias (especially chlorosis and leukemia), as well as in most cases of pneumonia and tuberculosis. According to Cabot,[42] a decided plaque increase favors thrombosis.

Hemokonia.—These are colorless, refractive spheres of about 1 μ in diameter, and endowed with active whirling (non-ameboid) motility. Hemokonia are possibly nothing more than free granules extruded from the neutrophile and eosinophile leukocytes, and may have some bearing on immunity. These so-called particles of "blood dust" have no real clinical meaning, but it is known that they are especially abundant in typhus fever and in Addison's disease.

IV. SPECIAL SURGICAL HEMATOLOGY.

Abscess.—An abscess from which free absorption of toxic material occurs sooner or later causes a *secondary anemia*, the degree of which roughly measures the virulence of the poison. Chronicity of the lesion, low-grade resistance by the individual, and well-marked toxemia are the three factors which do the greatest damage to the hemoglobin and erythrocytes. Neither the size nor the site of the abscess determines the grade of the associated blood deterioration, although, other things being equal, the anemia is likely to be greater in deeply seated large abscesses than in those of superficial situation and of small size. Of 305 abscesses examined at the German Hospital, 62 (20.3 per cent.) had 50 per cent. or less of hemoglobin, while 20 (6.5 per cent.) showed an erythrocyte count of 3,000,000 or lower.

Leukocytosis also is determined by the grade of the toxemia. It may fail to develop, or if present, may suddenly decline as the result of an overwhelming poisoning of the patient. It is also absent when no reaction is excited, either because the lesion is benign or because it is effectually walled in by a pyogenic membrane. Extension of a pus focus is betrayed by an increase in, and adequate drainage by a disappearance of, the original leukocytosis. This table shows the range of the leukocytosis in relation to the site of the abscess in 451 cases:

Site of Abscess.	Number of Cases.	Average.	Maximum.	Minimum.	Percentage of Cases with Leukocytosis.
Appendical	174	16,709	58,500	4,200	86.0
Pelvic	180	15,634	48,200	550	67.7
Renal	30	13,924	33,600	6,000	86.6
Superficial	32	13,600	17,850	4,800	78.1
Empyema	10	17,180	31,800	11,200	100.0
Cholecystic	9	18,891	21,200	9,500	88.8
Hepatic	8	14,922	23,400	9,300	75.0
Cerebral	8	11,428	18,500	6,800	75.0

In *general sepsis* the above changes also occur, but generally in a more conspicuous form. All cases of sepsis not showing leukocytosis are either very mild or exceedingly severe.

Iodophilia is also excited by the above factors of leukocytosis, but it is also seen in toxemia so marked as to stifle the cellular increase.

The association of leukocytosis, hyperinosis, and iodophilia points to pyogenic abscess rather than to tuberculosis exudate, gumma, hematoma, or benign neoplasm, and to purulent not serofibrinous inflammations. The blood is of no use in differentiating cerebral abscess, apoplexy, and acute meningitis, for each of these lesions may cause leukocytosis. An intense iodin reaction with high leukocytosis suggests that the patient, though decidedly toxic, is reacting adequately, while iodophilia with leukopenia indicates crippling of systemic resistance.

Sepsis, in contrast to enteric fever, malarial fever, and most cases of miliary tuberculosis, shows leukocytosis and a more rapidly developing anemia, but in distinguishing this quartette of infections blood cultures, the serum test, and search for the malarial parasite furnish the most important hematologic criteria. Iodophilia, it should be noted, may occur in all of these conditions.

Appendicitis.—Many cases of appendicitis are moderately *anemic*, and a few decidedly so, the change being attributable to the effect of sepsis and to the patient's debility, aside from the appendical lesion. In 139 German Hospital cases the hemoglobin averaged 69.5 per cent., and the erythrocytes, 4,295,955 per cubic millimeter.

The *leukocytes* are not increased in number in most cases of catarrhal appendicitis, yet occasionally a moderate rise (to 16.000 or 18.000) is met with, doubtless as the result of a circumscribed periappendical peritonitis. In appendicitis with abscess, gangrene, or general peritonitis well-marked

leukocytosis is the rule, except in fulminant cases and in those in which an appendical abscess is so thoroughly walled in by a pyogenic membrane that no toxins enter the circulation. These figures, relating to 250 cases in the German Hospital, illustrate the leukocyte range in these two general types of the disease:

	Non-purulent* (76 Cases).	Purulent† (174 Cases).
Average	9,247	16,709
Maximum	17,100	58,500
Minimum	1,600	4,200
Counts above 20,000	None.	40
Counts of 10,000, to 20,000	31	110
Counts below 10,000	45	24

From the above data it appears that *average* counts in purulent cases about equal the *maximum* counts in the non-purulent; that simple catarrhal appendicitis does not raise the count higher than 20,000, but, roughly speaking, one-fourth of all purulent cases do so; that normal or subnormal figures are not incompatible with suppuration, gangrene, and their sequels; and, finally, that counts below 20,000 are no sure index to the character of the appendical lesion.

Analysis of almost 900 cases of appendicitis in the German Hospital justifies the following general deductions as to the diagnostic and prognostic significance of the leukocyte range in this disease.‡ In non-operative cases leukocytosis appearing during the early days of the attack suggests peritonitis, but the development of a leukocytosis after the first week is more likely to be symptomatic of appendical abscess. The sudden exaggeration of a leukocytosis already established betrays extension of the local lesion or of peritonitis, while the sudden decline of the count, with increasing acuteness of the other symptoms, signifies severe, perhaps fatal, toxemia. A stationary leukocytosis, with trifling fluctuations of the maximal figure, occurs in localized abscess, the count declining as the pus disappears or as it becomes walled in, and rising as suppuration extends and the process becomes periappendical. After operation, with adequate drainage, the leukocytes fall to normal within a few days, but with incomplete drainage they remain high, as they do also in cases with persistent peritonitis and other septic complications of the original appendical inflammation.

A normal leukocyte count or a moderate increase may be symptomatic of (*a*) simple catarrhal appendicitis, (*b*) circumscribed walled-off appendical abscess, or (*c*) fulminant appendicitis with severe toxemia. A well-defined leukocytosis may be met with (*a*) in appendical abscess imper-

*Including catarrhal and interstitial forms, obliterative appendicitis, and fecal and other concretions.

†Including cases with abscess, gangrene, perforative peritonitis, sepsis, etc.

‡These deductions, it should be clearly understood, are invariably to be read in correlation with other phases of the clinical picture. The blood-count, like most other laboratory findings, is but the supplement of the bedside data, and to exploit it as a specific sign is to invite embarrassing clinical errors. It is quite as bad practice to diagnose appendicitis by leukocytosis alone, as it is to stamp every heart murmur as endocarditic, or all glycosurias as diabetic.

fectly delimited by a permeable pyogenic membrane, (*b*) in appendical gangrene, and (*c*) in peri-appendical and general peritonitis. Upon the interpretation of the leukocyte count under these diverse circumstances the question of iodophilia sometimes has an important bearing. In the absence of iodophilia it is quite safe to conclude that no serious lesion of the appendix is present, although a positive reaction does not invariably imply the existence of an active inflammation.

In differentiating appendicitis from other abdominal inflammations the blood gives little or no real help: in, for example, pyosalpinx, ovarian abscess, pyonephrosis, perinephritic abscess, hepatic abscess, gall-bladder empyema, cecal cancer, intestinal obstruction, and mesenteric thrombosis there may be identical degrees of leukocytosis and of iodophilia. The same statement applies with equal force, though not with equal frequency, to acute gastritis, renal and hepatic colics, and dysmenorrhea, which if provocative of active inflammatory changes, raise the number of leukocytes and render them sensitive to iodin. Lead colic, though it may excite leukocytosis, disfigures the erythrocytes with basophilic stippling, a change found only in appendicitis cases which are exceedingly anemic. Simple tapeworm, should it ape appendicitis, is generally betrayed by eosinophilia. Gastralgia, enteralgia, and ovaralgia cause neither quantitative nor qualitative changes in the leukocytes. Nephroptosis, ovarian cyst, and uncomplicated enteric fever may safely be excluded if the patient has a well-marked leukocyte increase.

Actinomycosis.—A low color-index anemia and well-defined leukocytosis occur in this disease, probably more as the result of secondary sepsis than of any specific infection by the ray fungus. Superficial lesions usually are productive of lower leukocyte counts than those deeply seated.

Anesthesia.—A trivial hemoglobin loss, moderate polycythemia due to blood concentration, and a slight increase in the number of leukocytes lasting for about twenty-four hours, follow *ether anesthesia*. According to Lerber,[45] the leukocyte count is above normal in 95 per cent. of cases, the gain amounting to about 4000 (Chadborne[46]) or 5000 (Da Costa; Kalteyer[47]) per cubic millimeter, and affecting all forms of cells proportionately.

In *chloroform narcosis* the blood changes are similar to those excited by ether, but they are more marked and persist longer. Solimei[48] found, after protracted chloroform narcosis, methemoglobinemia, a delay in the coagulation time, evidences of active hemolysis, and a diminution in the oxygen content of the blood.

The risk, real or reputed, of operating on a patient having a low percentage of hemoglobin has been discussed in a preceding section. (See p. 115.)

Anthrax.—The occasional detection of the anthrax bacillus in the peripheral blood is the only hematologic finding thus far reported. Nothing is known of the cellular changes, if any exist in this infection.

Burns.—Locke's studies[43] show that in persons severely burned marked polycythemia, high leukocytosis, and decided plaque increase

develop within a few hours after the accident. The leukocytes show degenerative changes marked in parallelism to the gravity of the injury, and myelocytes occur in small numbers.

Chloroma.—A normoblastic type of *anemia*, of progressive character, is found in chloroma, and in most instances high absolute *lymphocytosis* and the presence of many myelocytes and eosinophiles. Exceptionally, the lymphocytosis is simply relative. From lymphatic leukemia chloroma must be differentiated by objective symptoms, since the blood changes may be identical. In such instances one should recall Dock's belief,[44] that chloroma is simply a malignant, highly neoplastic form of leukemia. Graves's disease may show moderate relative lymphocytosis, but never a high absolute increase of the lymphocytes.

Cholelithiasis.—The blood changes found in cholelithiasis are referable to the associated jaundice and to inflammatory and septic complications. Thus, in cases with jaundice *slow coagulation* is the rule; in 28 such instances I found an average coagulation time of ten minutes and forty seconds, while in twelve cases without jaundice the average was five minutes and twenty-four seconds. It has not been proved that the delayed clotting of jaundice due to gall-stones predisposes to hemorrhage, though this is undoubtedly true of the toxic jaundice due to malignant disease of the biliary passages.

The *anemia* is seldom marked, except in septic cases, in which extremely low hemoglobin and erythrocyte figures are found. Of 136 hospital cases of gall-stone, the hemoglobin was 50 per cent. or less in 13 (9.5 per cent.), and the erythrocytes 3,000,000 per cubic millimeter or lower in 17 (12.5 per cent.).

Leukocytosis and *iodophilia* are rather common in gall-stone, owing to the frequency of complications. The former occurred in 35 (25.7 per cent.) of the above series, always as the result of marked jaundice, or of some complication, such as empyema of the gall-bladder, purulent and septic cholangitis, or peritonitis. The incidence, degree, and duration of the leukocyte changes are obviously determined by such factors as these.

A high leukocyte count suggests some complication of cholelithiasis; but a low count does not necessarily imply simple gall-stone, though when qualified by a negative iodin reaction such an inference is most strong. The blood is no criterion in distinguishing hepatic and renal colics.

Enteric Fever.—*Bacillemia*, a positive *serum reaction*, well defined secondary *anemia*, and *leukopenia* with lymphocytosis are the helpful hematologic findings in this infection. *Iodophilia* also develops in about one-half of all uncomplicated cases, and in practically all of those secondarily septic. To the surgeon this blood picture is of interest, first because of its bearing upon the initial diagnosis of typhoid; and, second, on account of its relation to the various surgical complications of the disease. The clinical pertinence of changes in the coagulation time of the blood in typhoid has already been noted. (See p. 112.)

Sepsis and trichiniasis are the two surgical diseases which perhaps most closely counterfeit enteric fever in their general symptomatology. But in septicemia blood cultures usually yield pyogenic cocci, the Widal test is

negative, leukocytosis is the rule, and the anemia is more acute in development and in degree. Trichiniasis is characterized by decided leukocytosis with eosinophilia, and by negative results from blood cultures and the serum test.

Of the intercurrent surgical complications which alter the blood picture of typhoid, hemorrhage, perforation, and secondary purulent and septic lesions are the most important. *Intestinal hemorrhage*, if severe, causes a prompt and appreciable exaggeration of the anemia already present, though in the great majority of instances the blood loss is not sufficiently great so to act. Leukocytosis develops in most cases within a few hours after the hemorrhage, and persists for a variable period, depending upon the extent of the bleeding and upon the patient's reaction. (See "Post-hemorrhagic Leukocytosis," p. 128.) *Intestinal perforation* excites leukocytosis, provided that the shock is not too great—a proviso which unfortunately robs this sign of diagnostic value in fully one-half of all cases. Aside from this, the cellular increase may be so transient as to escape detection, unless an almost hourly count is made. In Manges recent report[49] of sixteen cases of perforation with leukocyte counts, these cells rose in seven, of which three recovered; fell in three, all of which died; and remained practically unchanged in six, of which one recovered. These figures corroborate Thayer's earlier statement[50] that the prospect of relief from surgical interference is best in cases with leukocytosis, the absence or disappearance of which indicates malignancy of the infection and prostration of the patient. The rapid decline of a frank post-perforative leukocytosis, *pari passu* with an aggravation of the other symptoms, means a fulminant peritonitis plus a low ebb of the patient's vitality.

Of the secondary *purulent* and *septic lesions* exciting leukocytosis and intensifying iodophilia, the most important surgically are empyemata of the gall-bladder and of the thorax, suppurative arthritides, periostitis, osteomyelitis, purulent otitis media, mastoiditis, parotid bubo, septic thrombosis, and bed-sores. Complicating pneumonia and meningitis also affect the blood similarly.

Fractures.—In simple fractures a slight, transient *leukocytosis* sometimes develops, though more cases are encountered without this sign than with it; complicated fractures may give higher counts, which, however, do not exceed 15,000 or 16,000 per cubic millimeter, according to the experience of Blake, Hubbard, and Cabot.[51] *Lipemia* has been detected in fractures of the long bones lacerating the fatty marrow, with and without associated signs of fat embolism.

Hemorrhage.—*Oligemia* is the immediate consequence of an acute hemorrhage, and during this stage the blood, though of lessened volume, shows no corpuscular changes. *Hydremia* follows, as reaction sets in, and now the hemoglobin and erythrocyte values begin to fall, as the reëstablishment of the blood volume progresses by transfer of fluid from the tissues into the vessels. Even after this has occurred a further hemoglobin and erythrocyte loss takes place, so that several days elapse before the stable minimum of the anemia is attained. That an extraordinary degree of anemia after hemorrhage may be compatible with life

is shown by the complete recovery of Hayem's patient[52] with but 11 per cent. of erythrocytes, and of Béhier's[53] with 19 per cent. of cells, following uterine hemorrhages. Leukocytosis (*q. v.*), striking increase in the number of plaques, and acceleration of the clotting time are other post-hemorrhagic findings.

Regeneration of the blood, according to Bierfreund,[54] is complete within four weeks after the hemorrhage if the hemoglobin loss does not exceed 25 per cent., and within three weeks if it is not greater than 20 per cent. The duration of this period of blood repair depends upon many factors, of which the extent of the blood loss, the native reactive powers of the individual, and the question of associated disease are the most important. Transfusion hastens regeneration, and may even stimulate it so actively that the blood values mount higher than the maximum normal point (Hall and Eubank;[55] Otto[56]). As regeneration proceeds, the deficiency of erythrocytes is made up much more rapidly than the hemoglobin loss, so that a low color-index persists for some time after the hemorrhage. During the period of regeneration the cyclical appearance of large numbers of normoblasts, known as "blood crises," is thought to be a sign of active and normal hemogenesis, for these phenomena frequently are followed by substantial gains in the hemoglobin and cellular figures. Owing to the abnormally active type of hemogenesis incident to hemorrhage, many of the cells thrown into the blood-stream are faultily formed and highly vulnerable—hence the occurrence of deformed, hydropic, and atypically staining cells, especially during the early stages of the regeneration period.

In hemorrhage versus shock, the detection of a lowered blood density and a subnormal hemoglobin percentage suggests the former, while in the latter the specific gravity is increased and the hemoglobin value unaltered. These findings apply, of course, only to pure, uncomplicated types of these accidents, and are therefore seldom applicable in a clinical sense. Mummery,[57] Sherrington and Copeman,[58] and Malcolm[59] should be consulted for accounts of the blood changes secondary to shock.

Intestinal Obstruction.—Leukocytosis promptly develops after intestinal obstruction, being symptomatic either of autointoxication or of gangrene and peritonitis. Bloodgood[60] believes that a count of 20,000 or 30,000 three or four days after the beginning of symptoms is a favorable sign for operative interference, but that if the leukocytes are below 10,000 at this time, it is probable that extensive gangrene-peritonitis has occurred. As a rule, a high count during the first twenty-four hours of the obstruction, followed by an abrupt decline in the leukocytosis within the next day or two, is highly suggestive of peritonitis and gangrene, in the absence of which complications the count remains at its maximum for four or five days and then gradually falls to normal.

Jaundice.—The *slow clotting* of the blood in conditions of icterus has been sufficiently referred to elsewhere. (See p. 112.) In the Jefferson Hospital there are records of four fatal cases of post-operative hemorrhage in jaundice due to cancer of the bile-ducts. Simple catarrhal jaundice has little or no effect on the blood, the *anemia* being ordinarily trifling,

except in strikingly toxic cases, and the *leukocytes* normal in number in fully four-fifths of all cases. In forty cases I found seven (17.5 per cent.) with a hemoglobin percentage of 50 or less; nine (22.5 per cent.) with an erythrocyte count of 3,000,000 per cubic millimeter or lower; and eight (20 per cent.) with a leukocyte count in excess of 10,000 per cubic millimeter. Leukocytosis with jaundice suggests cholemia, pus, or cancer—not a simple inflammation of the biliary passages.

Malignant Disease.—A stubbornly persistent *anemia* is a hallmark of carcinosis, especially in its later stages, and in growths interfering with assimilation and nutrition, as in cancer of the esophagus and of the stomach. The hemolytic action of cancer toxins, discovered by Kullman,[72] explains the cachectic anemia of carcinoma not implicating organs directly concerned in body nutrition. Of one hundred and fifty-five cases of various types of carcinoma which I have analyzed, forty-five (29.0 per cent.) showed 50 per cent. or less of hemoglobin, and forty-three (27.7 per cent.) an erythrocyte count of 3,000,000 or lower. The average blood deterioration is more striking in carcinoma than in sarcoma, and in the individual case of the former far more conspicuous anemia frequently is encountered. Of forty-two sarcomata, but eight (19.2 per cent.) had a hemoglobin percentage of 50 or less, and only five (11.9 per cent.) an erythrocyte count of 3,000,000 or lower.

The *leukocytosis* of malignant disease is by no means constant, for it depends not so much upon the action of specific irritants as it does upon such factors as inflammation, sepsis, and hemorrhage. In my experience leukocytosis is almost twice as frequent in sarcoma as it is in carcinoma, 61.9 and 36.7 being the respective percentages of its incidence in the two types of tumors.

The following table shows the range of the leukocytes in one hundred and fifty-five cases of carcinoma:

Seat of Tumor.	Average.	Maximum.	Minimum.	Number with Leukocytosis.
Stomach, 75 cases.....	7,785	23,400	1,000	19 cases, or 25.3%
Uterus, 25 "	11,150	24,000	3,200	13 " " 52.0 "
Rectum, 16 "	8,921	16,000	6,000	4 " " 25.0 "
Breast, 18 "	10,163	31,500	5,200	6 " " 33.3 "
Liver, 10 "	17,549	40,800	8,000	8 " " 80.0 "
Intestine, 7 "	11,185	16,300	7,000	5 " " 71.4 "
Pancreas, 4 "	10,850	18,200	6,600	2 " " 50.0 "

From the above data it appears that the incidence and degree of leukocytosis are greatest in cancer of the liver, and least in cancer of the stomach and of the rectum. In gastric cancer *digestion leukocytosis* is absent in about 80 per cent. of all cases—a sign once believed to be of great diagnostic value in differentiating gastric cancer and ulcer, since in the latter digestion leukocytosis persists. The value of this sign is also negatived by the fact that it is occasionally absent in apparently healthy individuals and also in those suffering from various forms of gastritis.

In sarcoma leukocytosis occurred in twenty-six (61.9 per cent.) of forty-two cases examined, the average count being 12,386, the maximum 40,000, and the minimum 5000 per cubic millimeter. The general rule applies here (as it does in carcinoma) that small, inactive, superficial tumors show lower counts than large, active neoplasms implicating deep viscera.

Involvement of the bone-marrow by malignant disease is generally shown by well-defined *myelemia* and sometimes by *eosinophilia;* and of the lymphatic system, by *lymphocytosis.*

Other blood changes in malignant disease are the absence of *hyperinosis* and, in carcinoma, the presence of *hyperglycemia.* (See p. 120.) Loeper and Louste's claim,[61] that specific neoplastic cells invade the blood-stream in sarcoma, has not been corroborated; in no one of five cases have I been able to identify such cells.

In differentiating malignant and benign tumors the presence of persistent anemia and leukocytosis points to the former; abscess with sepsis may show identical findings, plus iodophilia and hyperinosis, which do not occur in malignant disease save in the event of septic complications. In malignant neoplasm of the liver versus amyloid disease, gumma, or Hanot's cirrhosis, high leukocytosis suggests the first; if hydatid disease exists, a high eosinophilia usually is found. The blood is an uncertain means of distinguishing cancer and ulcer of the stomach, although long-continued leukocytosis indicates cancer, since it occurs in gastric ulcer only as the result of digestion, of hemorrhage, and of perforation; high-grade anemia is also more common in cancer than in ulcer. The cachexias of malignant disease and of pernicious anemia are sometimes very similar, though the blood pictures differ, a high color-index, marked oligocythemia with megaloblasts predominating, and leukopenia with relative lymphocytosis being characteristic of the primary type of anemia.

Peritonitis.—Septic peritonitis constantly provokes *leukocytosis,* except in the mildest and in the severest cases; in the latter, however, *iodophilia* is most intense. Tuberculous peritonitis, except in early childhood, never causes a rise in the leukocyte count. The highest leukocytoses are found in purulent inflammations of the peritoneum, and in these high-grade secondary *anemia* also tends to appear. Of fifty-four cases of non-tuberculous peritonitis examined by me, forty-two (77.7 per cent.) showed frank leukocytosis, and forty (74.0 per cent.) well-marked anemia. The clinical pertinence of the leukocyte count in the peritonitides of enteric fever and of appendicitis is referred to under these diseases.

Protozoan and Helminthic Infections.—Malarial Fever.—Aside from the presence of specific hematozoa in the blood-stream, the malarial infections are characterized by anemia of variable intensity, by absence of leukocytosis, and by melanemia. The *malarial hematozoa* are animal parasites which invade the erythrocytes of the infected individual and there undergo an asexual phase of development ending in the destruction of their cellular hosts, in the liberation of newly developed parasites, and in the evolution of forms destined to be imbibed by the mosquito

(*Anopheles*), in which insect they pursue a sexual developmental phase essential for their perpetuation. *Anemia*, due to the destruction of the parasitiferous cells and to the specific malarial poison, develops in all cases, and, according to the severity of the infection and its chronicity, attains a variable degree of intensity. The *leukocytes*, save for the transient rises attending the paroxysms, are not increased in number; they are, indeed, usually subnormal, and show a decided relative lymphocytosis. *Pigment*, both within the leukocytes and extracellular, is a distinctive finding in most cases of malaria.

The foregoing blood picture serves to distinguish malarial fever from sepsis, in which infection pyogenic coccemia, leukocytosis, and iodophilia give the sought-for clues. In differentiating malarial fever from enteric fever and from tuberculosis, each of which may induce blood changes identical with those of ague, information may be derived from blood cultures and from the serum test.

Filariasis.—The peripheral blood of individuals suffering from filariasis is infested with embryos of the *Filaria sanguinis hominis* bred by parental forms of the parasite lodged in some part of the deep lymphatic system. These embryos are graceful, delicate worms, consisting of a central granular body enveloped by a loose hyaline sheath, and possessing active motility, owing to which they incessantly move about in the plasma between the masses of blood-corpuscles. Like the malarial parasite, the filaria requires the mosquito (*Culex fatigans*) as an intermediate host, to insure its perpetuation. In the commonest variety of filariasis, due to the *Filaria nocturna*, the embryos cyclically invade the peripheral blood during the subject's resting hours, but retire to the deep circulation when he actively moves about.

Fig. 29.—Filaria Sanguinis Hominis. Fresh blood film, showing granular degeneration of the parasite.

Anemia, when present, is traceable to some associated lesion, for the filariæ neither mechanically nor toxically affect the erythrocytes. The *leukocytes* show conspicuous changes—leukocytosis plus eosinophilia, each of which is marked in relation to the novelty of the infection, and tends to disappear in patients who have harbored the worms for some time.

The blood examination affords a means of differentiating filarial from idiopathic chyluria; lymph scrotum from hydrocele; filarial orchitis from other testicular inflammations; and hernia from filarial tumors of the groin. True elephantiasis Arabum, since it seldom causes a parasitemia, can rarely be distinguished from non-parasitic lymphedema by the blood, though a leukocytosis and an eosinophile increase are suggestive of the filarial form of the disease.

Trichiniasis.—*Leukocytosis* and *eosinophilia* constitute the hematologic formula of trichina infection, which of itself does not produce *anemia*. Eosinophilia, however, may be absent, as I have shown,[62] should the infection be so malignant as to suppress proliferation of the eosinophiles in the marrow, and it may disappear in cases of long standing, as in other forms of helminthiasis. Schleip's masterly monograph[63] should be consulted for the most comprehensive account of this subject.

The detection of an eosinophile leukocytosis serves to identify cases of trichiniasis otherwise symptomless, and to discriminate between those which resemble other infections, notably enteric fever. Absence of eosinophilia, on the other hand, is no criterion for ruling out trichiniasis.

Echinococciasis.—Like trichiniasis, hydatid disease causes an *eosinophile leukocytosis* without a specific anemia, no matter where the cysts may be situated. These changes promptly disappear after thorough evacuation of the cysts, and they gradually fade away in time, in cases not brought to the knife. Diagnostically, the above blood findings are of value in distinguishing hydatid tumors from pyogenic abscess and from solid tumors, provided that other factors of eosinophilia can be excluded.

Trypanosomiasis.—The demonstration of trypanosomata in the blood of human beings affected with tropical splenomegaly, sleeping sickness, and various cachexial fevers native to warm countries, has marked a brilliant advance in tropical medicine.* The parasite of man, termed *Trypanosoma gambiense*, is an actively motile protozoön, the body of which is provided with a delicate undulatory membrane and a whip-like flagellum.† The cultivation of trypanosomata *in vitro* from the Leishman-Donovan bodies of kala-azar, lately accomplished by Rogers[64] and by Chatterjee,[65] suggests the biologic entity of these two organisms.

Fig. 30.—Trypanosoma Gambiense.
(From a Leishman-stained specimen, furnished by the late Dr. J. Everett Dutton.)

*The subject of human trypanosomiasis is inseparably associated with the name of J. Everett Dutton, who first discovered the organism in the blood of man, and adequately described its relation to disease. The recent untimely death of Dr. Dutton, while pursuing his investigations in the heart of the Congo region, has added another name to that noble roll of martyrs to science whose lives pay toll in the march of knowledge.

†For detailed descriptions of trypanosomiasis and its organism see the following important contributions: (1) *Nepveu:* "Compt. rend. Soc. biol.," Paris, 1898, v, 1172. (2) *Forde:* "Journ. Trop. Med.," 1902, v, 261. (3) *Dutton:* Brit. Med. Journ.," 1902, ii, 881. (4) *Dutton and Todd:* "Lancet," 1903, ii, 1727. (5) *Laveran:* "Compt. rend. Acad. d. sc.," Paris, 1904, cxxxviii, 841. (6) *Castellani:* "Brit. Med. Journ.," 1903, i, 1218, 1431. (7) *Koch:* "Brit. Med. Journ.," 1904, ii, 1445. (8) *Thomas:* "Brit. Med. Journ.," 1905, i, 1140. (9) *Rogers:* "Lancet," 1905, i, 1484. (10) *Bruce, Nebarro, Greig:* "Brit. Med. Journ.," 1903, ii, 1343. (11) *Dutton, Todd, Christy:* "Brit. Med. Journ.," 1904, i, 186; ii, 369. (12) "The Thompson Yates and Johnston Lab. Rep.," 1905, vi, 1. (13) *Greig, Gray:* "Reports of the Sleeping Sickness Commission of the Royal Society," London, 1905, v, 1.

Trypanosomiasis is accompanied by well-marked *anemia* and by relative *lymphocytosis* without leukocytosis—the same changes incident to malarial fever. The distinction, then, between these two types of protozoan infection rests upon the detection of the specific hematozoön.

Other Protozoan Diseases.—In amebiasis attended by hepatic abscess leukocytosis with more or less anemia develops, as in other suppurative states. In Schlayer's eleven cases[66] the leukocyte counts averaged 25,000, and in Futcher's[67] fifteen, 18,350 per cubic millimeter, but Osler[68] found that much lower figures were compatible with pus. In the question of malarial fever versus the intermittent pyrexia of hepatic amebic abscess, frank leukocytosis practically excludes paludism.

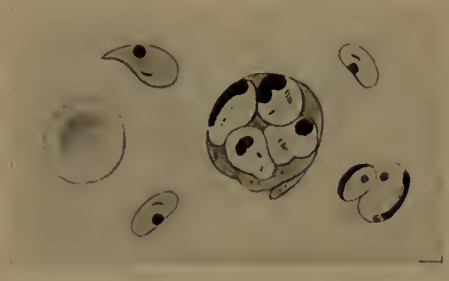

Fig. 31.—Leishman-Donovan Bodies.

Other infections, such as kala-azar and the various intestinal helminthiases, have no special surgical pertinence. It is of interest, however, to note that all forms of intestinal worms are capable of provoking marked eosinophilia, and that some forms (notably the *Bothriocephalus latus* and the *Uncinaria duodenale*) set up anemia of a most striking type.

Syphilis.—The *Treponema pallidum* of Schaudinn and Hoffmann,[69] which possibly is the specific cause of syphilis, has been found not only in the local lesions of the disease, but also in the blood of the spleen and of the general circulation of luetic subjects. Siegel's *Cytorrhyctes luis*[70] is another supposed hematozoön which at present enjoys a certain vogue as the long-sought factor of syphilis. Of these two "organisms," Schaudinn's deserves the greater confidence. Siegel's cytorrhyctes strongly reminds one of those forms of dwarfed and fragmented erythrocytes found in anemic blood, especially in specimens which have remained exposed to the air for any length of time.

The *anemia* which exists in all cases of syphilis varies with the intensity and chronicity of the infection and with the effect of the specific treatment on the individual. In general terms it may be stated that in the primary stage of the adequately treated case the blood changes are like those of chlorosis, and that in the secondary stage moderate secondary anemia develops. In a neglected case of tertiary lues excessive blood impoverishment occasionally is found—the so-called "syphilitic pernicious anemia." Mercury, when administered for a fortnight or so, improves a syphilitic anemia, but when given continuously for a longer period it tends to act hemolytically, and therefore to aggravate the anemia. Marked hemoglobin deficiency in a mercurialized patient prognosticates intense symptoms as the disease matures. *Justus's reaction*,[71] a decided hemoglobin loss a few hours after a single inunction of mercury in a case of untreated syphilis, is in no wise pathognomonic. It sometimes fails to occur in early initial lesions, in undoubted secondary syphilis, and in latent cases; it may be positive in certain other non-syphilitic diseases.

Moderate *leukocytosis* sets in during the secondary stage, and in the

anemia of tertiary syphilis a decided relative lymphocytosis is common, often associated with numerous myelocytes and perhaps with eosinophilia. In cases with high-grade anemia I have constantly detected *iodophilia.*

In distinguishing a severe syphilitic anemia from true pernicious anemia, the absence of a high color-index and of megaloblastic changes are sufficient to rule out the latter.

Tuberculosis.—The blood changes found in tuberculosis are referable to the influence of such factors as secondary pyogenic infection, malnutrition, and drains upon the body albumins, rather than to the disease itself, for a pure infection with Koch's tubercle bacillus causes practically no changes in the composition of the blood, save in the two exceptions noted below. The presence of *anemia* and *leukocytosis* in a tuberculous individual therefore suggests the existence of a secondary septic infection. A case of simple tuberculous adenitis shows a normal blood count, but so soon as the lesions soften and fistulate and become septic, the hemoglobin and erythrocytes begin to decline, the leukocytes to rise, and iodophilia to appear. The same is true when a secondary infection attacks a tuberculous hip, spine, kidney, or lung, none of which lesions in the absence of complications shows these blood changes. Unlike these forms of pure tubercle infection, tuberculosis of the meninges and, in the young child, of the peritoneum commonly excites well-defined leukocytosis during its acute phases.

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